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L4 ANSWER 1 OF 5 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001142621 EMBASE

TITLE: Bone induction by BMPs/OPs and related family members in primates: The critical role of delivery systems.

AUTHOR: Ripamonti U.; Ramoshebi L.N.; Matsaba T.; Tasker J.; Crooks J.; Teare J.

CORPORATE SOURCE: Dr. U. Ripamonti, Bone Research Unit, MRC/University of the

Witwatersrand, 7 York Road, Parktown 2193, Johannesburg, South Africa. 177ripa@chiron.wits.ac.za

SOURCE: Journal of Bone and Joint Surgery - Series A, (2001) 83/SUPPL. 1 II (S1116-S1127).

Refs: 60

ISSN: 0021-9355 CODEN: JBJSA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 021 Developmental Biology and Teratology  
033 Orthopedic Surgery  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Background: In a series of studies in the primate *Papio ursinus*, we have examined the capacity of bone morphogenetic proteins (BMPs/OPs) delivered in a variety of biomaterial carrier systems to elicit bone formation in heterotopic and orthotopic sites. In this review, we compare the osteoinductive effects of different biomaterial delivery systems that

have

or have not been pretreated with BMPs/OPs. In particular, we focus on the geometric induction of bone formation by sintered porous hydroxyapatite (SPHA) discs with concavities on their planar surfaces, which elicit bone formation without exogenously applied BMPs/OPs. Methods: Heterotopic bone formation was examined by bilaterally implanting 100-mg pellets of a collagenous carrier containing BMPs/OPs in the rectus abdominis muscle of the adult baboon. Orthotopic bone formation was examined by implanting 1

g

of a collagenous carrier containing BMPs/OPs into two full-thickness critical-sized 25-mm-diameter defects on each side of the calvaria of adult baboons. The BMPs/OPs whose effects were examined included recombinant human osteogenic protein-1 (rhOP-1), recombinant human transforming growth factor-.beta.1 (rhTGF-.beta.1), rhTGF-.beta.2, and porcine platelet derived transforming growth factor-.beta.1 (pTGF-.beta.1). Tissue from the rectus abdominis muscle was harvested 30 or 90 days after implantation. Tissue from the orthotopic calvarial model

was examined at 1, 3, 6, 9, and 12 months after implantation. To demonstrate the effect of surface geometry on bone induction, hydroxyapatite powders were sintered to form solid discs with a series of concavities on the planar surfaces of the SPHA discs. The discs were either pretreated with exogenous rhOP-1 or not treated with exogenous OP-1. They were then implanted heterotopically or orthotopically into calvarial defects. Bone formation was evaluated histologically in undecalcified sections stained with Goldner's trichrome stain or 0.1% toluidine blue. Results: Naturally derived BMPs/OPs or rhOP-1 in a collagenous carrier elicit heterotopic bone formation and the complete healing of 25-mm-diameter critical-sized defects by day 90 following implantation. Binary applications of TGF- $\beta$ .1 together with rhOP-1 in the collagen carrier induced massive endochondral ossicles in heterotopic sites and bone formation in calvarial defects, pTGF- $\beta$ .1, rhTGF- $\beta$ .1, and rhTGF- $\beta$ .2 are powerful inducers of heterotopic endochondral bone formation but elicit limited bone formation in

calvarial

defects. SPHA discs pretreated with rhOP-1 elicited extensive bone formation in both heterotopic and orthotopic sites. However, SPHA without rhOP-1 also elicited bone formation in heterotopic and orthotopic sites and complete healing of the calvarial defects. Conclusion: We have prepared SPHA discs with concavities on their planar surfaces that induce bone formation in heterotopic or orthotopic critical-sized calvarial defects without exogenously applied BMPs/OPs. This biomaterial induces bone formation by intrinsic osteoinductivity regulated by the geometry of the substratum. The incorporation of specific biological activities into biomaterials by manipulating the geometry of the substratum, defined as geometric induction of bone formation, may make it possible to engineer morphogenetic responses for therapeutic osteogenesis in clinical

contexts.

Clinical Relevance: We have implemented a clinical trial using naturally derived BMPs/OPs extracted and purified from bovine bone matrices and implanted in craniofacial defects in humans. In addition, the discovery that specific geometric and surface characteristics of sintered hydroxyapatites can induce intrinsic osteoinductivity in primates paves the way for formulation and therapeutic application of porous substrata designed to obtain predictable intrinsic osteoinductivity in clinical contexts.

L4 ANSWER 2 OF 5 MEDLINE DUPLICATE 1  
ACCESSION NUMBER: 2001221630 MEDLINE  
DOCUMENT NUMBER: 21209732 PubMed ID: 11314789  
TITLE: Bone induction by BMPs/OPs and related family members in primates.  
AUTHOR: Ripamonti U; Ramoshebi L N; Matsaba T; Tasker J; Crooks J; Teare J  
CORPORATE SOURCE: Bone Research Unit, South African Medical Research Council/University of the Witwatersrand, Medical School, Johannesburg.. 177ripa@chiron.wits.ac.za  
SOURCE: JOURNAL OF BONE AND JOINT SURGERY. AMERICAN VOLUME, (2001) 83-A Suppl 1 (Pt 2) S116-27.  
Journal code: HJR; 0014030. ISSN: 0021-9355.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 200105  
ENTRY DATE: Entered STN: 20010517  
Last Updated on STN: 20010517  
Entered PubMed: 20010420  
Entered Medline: 20010503

AB BACKGROUND: In a series of studies in the primate *Papio ursinus*, we have examined the capacity of bone morphogenetic proteins (BMPs/OPs) delivered in a variety of biomaterial carrier systems to elicit bone formation in heterotopic and orthotopic sites. In this review, we compare the osteoinductive effects of different biomaterial delivery systems that have

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of the SPHA discs. The discs were either pretreated with exogenous rhOP-1 or not treated with exogenous OP-1. They were then implanted heterotopically or orthotopically into calvarial defects. Bone formation was evaluated histologically in undecalcified sections stained with Goldner's trichrome stain or 0.1% toluidine blue. RESULTS: Naturally derived BMPs/OPs or rhOP-1 in a collagenous carrier elicit heterotopic bone formation and the complete healing of 25-mm-diameter critical-sized defects by day 90 following implantation. Binary applications of TGF-beta1 together with rhOP-1 in the collagen carrier induced massive endochondral ossicles in heterotopic sites and bone formation in calvarial defects. pTGF-beta1, rhTGF-beta1, and rhTGF-beta2 are powerful inducers of heterotopic endochondral bone formation but elicit limited bone formation in calvarial

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CLINICAL RELEVANCE: We have implemented a clinical trial using naturally derived BMPs/OPs extracted and purified from bovine bone matrices and implanted in craniofacial defects in humans. In addition, the discovery that specific geometric and surface characteristics of sintered hydroxyapatites can induce intrinsic osteoinductivity in primates paves the way for formulation and therapeutic application of porous substrata designed to obtain predictable intrinsic osteoinductivity in clinical contexts.

L4 ANSWER 3 OF 5 CANCERLIT  
ACCESSION NUMBER: 2001209732 CANCERLIT  
DOCUMENT NUMBER: 21209732  
TITLE: Bone induction by BMPs/OPs and related family members in primates.  
AUTHOR: **Ripamonti U; Ramoshebi L N;** Matsaba T; Tasker J; Crooks J; Teare J  
CORPORATE SOURCE: Bone Research Unit, South African Medical Research Council/University of the Witwatersrand, Medical School, Johannesburg. 177ripa@chiron.wits.ac.za  
SOURCE: JOURNAL OF BONE AND JOINT SURGERY. AMERICAN VOLUME, (2001).

83-A Suppl., Vol. 1, Pt. 2, pp. S116-27.

Journal code: HJR. ISSN: 0021-9355.

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
FILE SEGMENT: MEDL; L; Abridged Index Medicus Journals; I  
LANGUAGE: English  
OTHER SOURCE: MEDLINE 21209732  
ENTRY MONTH: 200104

AB BACKGROUND: In a series of studies in the primate *Papio ursinus*, we have examined the capacity of bone morphogenetic proteins (BMPs/OPs) delivered in a variety of biomaterial carrier systems to elicit bone formation in heterotopic and orthotopic sites. In this review, we compare the osteoinductive effects of different biomaterial delivery systems that

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of a collagenous carrier containing BMPs/OPs into two full-thickness critical-sized 25-mm-diameter defects on each side of the calvaria of adult baboons. The BMPs/OPs whose effects were examined included recombinant human osteogenic protein-1 (rhOP-1), recombinant human transforming growth factor-beta1 (rhTGF-beta1), rhTGF-beta2, and porcine platelet derived transforming growth factor-beta1 (pTGF-beta1). Tissue from the rectus abdominis muscle was harvested 30 or 90 days after implantation. Tissue from the orthotopic calvarial model was examined at 1, 3, 6, 9, and 12 months after implantation. To demonstrate the effect

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calvarial

defects. SPHA discs pretreated with rhOP-1 elicited extensive bone

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CLINICAL RELEVANCE: We have implemented a clinical trial using naturally derived BMPs/OPs extracted and purified from bovine bone matrices and implanted in craniofacial defects in humans. In addition, the discovery that specific geometric and surface characteristics of sintered hydroxyapatites can induce intrinsic osteoinductivity in primates paves the way for formulation and therapeutic application of porous substrata designed to obtain predictable intrinsic osteoinductivity in clinical contexts.

L4 ANSWER 4 OF 5 MEDLINE DUPLICATE 2  
ACCESSION NUMBER: 2000225398 MEDLINE  
DOCUMENT NUMBER: 20225398 PubMed ID: 10760748  
TITLE: Osteogenic protein-1, a bone morphogenetic protein,  
induces angiogenesis in the chick chorioallantoic membrane and synergizes with basic fibroblast growth factor and transforming growth factor-beta1.  
AUTHOR: Ramoshebi L N; Ripamonti U  
CORPORATE SOURCE: Bone Research Laboratory, Medical Research Council/University of the Witwatersrand, Medical School, Johannesburg 2193, South Africa.. natr@chiron.wits.ac.za  
SOURCE: ANATOMICAL RECORD, (2000 May 1) 259 (1) 97-107.  
Journal code: 4QM; 0370540. ISSN: 0003-276X.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200006  
ENTRY DATE: Entered STN: 20000706  
Last Updated on STN: 20000706  
Entered Medline: 20000623  
AB Capillary invasion is a vital regulatory signal during bone morphogenesis that is influenced by angiogenic molecules such as fibroblast growth factor (FGF) and some members of the transforming growth factor-beta (TGF-beta) superfamily, including TGF-betas themselves. Bone morphogenetic proteins (BMPs), which are members of the TGF-beta superfamily, have previously not been shown to possess direct angiogenic properties. Osteogenic protein-1 (OP-1; BMP-7) is a potent regulator of cartilage and bone differentiation in vivo. The osteogenic and angiogenic properties of OP-1 at both ortho- and heterotopic sites in adult chacma baboons (*Papio ursinus*) are enhanced synergistically by the simultaneous application of relatively low doses of TGF-beta1. The single application of relatively high doses of TGF-beta1 (20 ng), and bFGF (500 ng) or relatively low (100 ng) and high (1,000 ng) doses of OP-1 in the chick chorioallantoic membrane (CAM) assay elicited a prominent and (for OP-1) dose-dependent angiogenic response. The binary application of a relatively low dose of OP-1 (100 ng) with a relatively low dose of bFGF (100 ng) or with a relatively low (5 ng) or high (20 ng) dose of TGF-beta1 resulted in a

synergistic enhancement of the angiogenic response. The angiogenic effect of the relatively low doses of the combined morphogens was distinctly more pronounced than that of the single application of the relatively high doses of the respective factors. The present findings suggest that these morphogens may be deployed in binary combination in order to accentuate experimental angiogenesis. The cooperative interaction of the different morphogens in the CAM assay may provide important biological clues towards the control of clinical angiogenesis.  
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L4 ANSWER 5 OF 5 MEDLINE DUPLICATE 3  
ACCESSION NUMBER: 1999443225 MEDLINE  
DOCUMENT NUMBER: 99443225 PubMed ID: 10515202  
TITLE: Immunolocalization of Bone Morphogenetic Protein-2 and -3 and Osteogenic Protein-1 during murine tooth root morphogenesis and in other craniofacial structures.  
AUTHOR: Thomadakis G; Ramoshebi L N; Crooks J; Rueger D C; Ripamonti U  
CORPORATE SOURCE: Bone Research Laboratory, Medical Research Council/University of the Witwatersrand, Medical School, Johannesburg, South Africa.  
SOURCE: EUROPEAN JOURNAL OF ORAL SCIENCES, (1999 Oct) 107 (5) 368-77.  
JOURNAL CODE: CBQ; 9504563. ISSN: 0909-8836.  
PUB. COUNTRY: Denmark  
JOURNAL; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Dental Journals; Priority Journals  
ENTRY MONTH: 199912  
ENTRY DATE: Entered STN: 20000113  
Last Updated on STN: 20000113  
Entered Medline: 19991220  
AB The distribution of Bone Morphogenetic Protein-2, and -3 (BMP-2 and BMP-3) and Osteogenic Protein-1 (OP-1, also known as BMP-7) during root morphogenesis and in other craniofacial structures was examined in sections of 12- to 18-d-old mouse heads using polyclonal and monoclonal antibodies. BMP-3 and OP-1 were localized in alveolar bone, cementum, and periodontal ligament, whereas BMP-2 was only localized in the alveolar bone of periodontium. All three BMPs were localized in predentine, dentine, odontoblasts, osteoblasts, osteocytes, osteoid, cartilage, chondrocytes and spiral limbus. BMP-2 and OP-1 were also localized in spiral ligament and interdental cells of the cochlea, whilst BMP-3 was restricted to the spiral ganglion. BMP-3 was also localized in ducts of submandibular and sublingual salivary glands, acini of the lacrimal gland, Purkinje cells in the cerebellum, nerve fibres of the cerebellum and brain, afferent cells of the dorsal root ganglia, inferior alveolar nerve, and peripheral processes of the vestibulocochlear nerve. OP-1 was also localized in hair and whisker follicles, sclera of the eye and in ameloblasts. The demonstration of BMP-3 in the nervous system suggests that this protein may be neurotrophic during development and maintenance of the nervous system. The composite expression of BMPs/OPs during periodontal tissue morphogenesis suggests that optimal therapeutic regeneration may entail the combined use of different BMPs/OPs.

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USPT,PGPB,JPAB,EPAB,DWPI,TDBD	l13 and (angiogen.clm.)	0	<u>L15</u>
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USPT,PGPB,JPAB,EPAB,DWPI,TDBD	l8 and l4	56	<u>L9</u>
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	(osteogenic adj protein) OR OP-1	474	<u>L8</u>
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	l6 and l4	157	<u>L7</u>
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	OP-1 or BMP\$	2022	<u>L6</u>
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	l1 and l4	0	<u>L5</u>
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	angiogen\$	6023	<u>L4</u>
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	Ramoshebi.in.	0	<u>L3</u>
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	Ramoshebi-L\$.in.	0	<u>L2</u>
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	Ripamonti-u\$.in.	13	<u>L1</u>

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